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Title: Non-Operative pain management interventions in patients with Intermittent Claudication: A protocol for a systematic mixed studies review with meta-analysis.

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ABSTRACT

Background/Aim: Intermittent claudication (IC) due to peripheral arterial disease (PAD) decreases individuals' capacity to engage in physical activity. Identifying effective components of pain management interventions in this population will be of potential value because pain is the main symptom limiting physical activity participation. This review will assess the components of pain management intervention that improve PA in patients with IC.

Methods: CINAHL, Cochrane Library, Ovid, ProQuest, AMED, MEDLINE, PsycINFO, Web of Science Core Collection, ScienceDirect, and PEDRO databases as well as grey literature will be searched until January 2016. Studies that investigated the effect of pain management interventions in patients with IC, or studies that investigated patients' perceptions to or experience with this intervention will be included. Papers will be screened by two authors to identify eligible studies and to assess study quality. Homogenous quantitative outcome data will be analysed using a random effects model of meta-analysis with results presented as relative risk for dichotomous outcomes and weighted mean or standardised mean for continuous outcomes. Qualitative data will be analysed using thematic synthesis.

Expected outcome: The systematic review will make recommendation on the effective components of pain management interventions to improve the physical activity of individuals with IC. This will guide the development of future interventions using the components identified to facilitate effectiveness.

INTRODUCTION

Peripheral Arterial Disease (PAD) is a clinical manifestation of atherosclerosis, and most commonly presents with a symptom of intermittent claudication (IC). IC, defined as exertion related ischaemic pain in the lower limb(s) experienced during walking and relieved by rest, is a debilitating condition which limits individuals' ability to walk and perform personal, social and occupational activities of daily life [2-4]. This is reported to affect 4.5% of all men and women aged 55-74 years [1]. The implications are that patients with IC suffer mobility impairment and loss of control [6], with a consequent decrease in health status, quality of life [2-5], and loss of social functions [6]. Additionally, the resultant decreased ability to engage in physical activity potentially leads to a further increase in the risk of cardiovascular events in a vascular system already compromised by PAD. Current epidemiological reports show PAD prevalence has increased by 13% in the last decade [7].

Despite the fact that pain has been identified as a key barrier to walking in IC [8], research into the effect of analgesic interventions for IC has remained largely inconclusive. Although some evidence supports the use of antiplatelet therapy [9-11], there are inconsistencies and a lack of clinically worthwhile efficacy in many other reports [12-16]. Transcutaneous Electrical Nerve Stimulation (TENS) is an electrotherapeutic modality commonly used in physiotherapy to manage pain. TENS is believed to accomplish pain reduction by stimulating the large non-nociceptive afferent (Aß) fibres leading to pain gating [17]. Despite the fact that TENS is inexpensive, safe, has minimal side-effects, and can be used by patients without supervision [18], there is minimal literature that investigates the use of TENS in individuals with IC. Seenan et al. demonstrated that TENS, specifically High Frequency-TENS, reduced lower limb ischaemic pain in healthy volunteers [19] and increased the walking performance of patients with IC in laboratory settings [20]. But whether improved walking capacity could be translated into free-living walking, described as "the level of walking that the individuals,

within their physical limitations, at their own pace, and in their own environment, typically perform" [21], has yet to be demonstrated.

Generally, conservative non-operative therapies that target pain relief, and which could be implemented in a clinical setting have been identified [20,22]. This, perhaps, makes it possible to identify an intervention, a modality or a combination that could be applied to relieve pain and increase physical activity in individuals with IC. However, differences in intervention setting (hospital vs home/community based), study design (RCTs vs non-RCTs), and intervention type, among other factors, may influence the success of an intervention. To date, evidence from non-operative pain management interventions targeting physical activity improvement among patients with IC has not been systematically evaluated. Therefore, there is currently no consensus regarding interventions centred on this pain management to improve physical activity in patients with IC. To develop a potentially effective intervention in pain management targeted at improving physical activity, a clear understanding of the components required for effectiveness and/or optimum patients' adherence to these interventions is needed. A systematic review of the literature is warranted to explore both quantitative and qualitative research evidence and determine the effective components of pain management interventions for improving physical activity for patients with PAD and IC. The proposed review will mainly seek to address the question of "what constitutes the effective components of pain management interventions to improve physical activity in patients with IC based on reports from published literature?". To achieve this, two secondary research questions relating to effectiveness of pain management interventions in patients with IC?", as well as patient experiences and perceptions to these interventions need to be investigated. This article details the protocol for a systematic review that aims to determine the effective components of non-operative pain management for improving physical activity in patients with PAD and IC. Specific objectives will include: 1) To determine effectiveness

of pain management interventions in patients with IC, and 2) To investigate experiences or perspectives to pain management interventions in patients with IC. The protocol for this systematic mixed studies review will be described according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocol (PRISMA-P) 2015 guidelines [23,24].

METHODS

Design

The protocol for this review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42015027912). The review method will use a two stage mixed studies review design. Studies meeting prior broad eligibility criteria will be included in the review and described in stage one. Then, stage two will involve further review of studies meeting narrower criteria, potentially pooling their data for a meta-analysis.

Eligibility Criteria

Decisions regarding eligibility of studies for inclusion in this review are described in terms of types of participants, types of study, intervention types, and types of outcomes in studies in line with PRISMA-P guideline. These criteria are based on literatures related to diagnostic for IC [2-4], as well as adaptation of inclusion criteria from previous reviews on other forms of interventions in individuals with intermittent claudication [25,26].

Types of participants

Studies involving adults of ≥18 years old participants with PAD and IC will be included. The review criteria will exclude participants without symptomatic IC. The basis for the diagnosis of IC may be objective, by use of questionnaire or clinically if objective measures were not used or reported. Either an ankle brachial index (ABI) < 0.9 or evidence of PAD on Doppler ultrasound or angiography will be judged sufficient for objective diagnoses of IC . No particular restrictions will be considered regarding settings of studies to be included.

Therefore, studies conducted in health centres, clinics, hospitals or community settings will be included.

Types of studies

Original research manuscripts in the English language, published in peer review journals, and conference proceedings will be included. There will be no restrictions on the types of study design eligible for inclusion. Accordingly both RCTs and non-RCTs will be included as long as they included at least one of these objectives: evaluated the effects of pain management in patients with IC; investigated the factors that influence adherence to these interventions; or the factors that influence the effectiveness of the interventions; evaluated patient experiences or perceptions of these interventions. Any type of control will be included, as well as pretest-posttest studies without a control. Both feasibility and pilot studies will be included. Also both studies published as full length article or abstract will be included. In all cases effort will be made to get data in a form that will enable analyses if not provided in the original publication.

Types of interventions

Pain management interventions for patients with PAD and IC will be considered for inclusion. Inclusion will not be restricted to a particular form, dose, frequency, intensity, duration of intervention or follow up period after intervention. For many patients, the intervention may be complex, incorporating other interventions such as, exercise and physical activity, medication, nutrition, psychological interventions, social interventions, or patient support, in addition to the pain management. Such studies will be included as long as the effect of the pain management intervention can be determined.

Types of outcome measures

Primary outcome measures will include pain intensity. Secondary outcomes will be physical activity capacity (e.g. walking time to onset of pain, pain free walking distance, maximum walking time, maximal walking distance); or free living physical activity (e.g. number of steps taken, time spent walking, cadence/speed of walking). Both subjective and objective measures of physical activity will be included. Also be assessed are other clinical outcomes such as: psychological outcomes (including factors such as self-efficacy, confidence, self-esteem, social functioning and coping); patients' perspective (responses to question on patient perception of interventions); quality of life. These secondary outcomes were chosen because they may be helpful in explaining the impact of pain outcome on physical activity improvement. This will enable decision regarding effective components for future designs of interventions. All outcome variables will be collected, analysed, graded and reported as they are reported in individual studies without altering the original description.

Exclusion criteria

Studies will be excluded if they were not primarily designed to target reduction of pain (even when pain reduction was reported), or did not explore patients' perception of intervention primarily designed for pain reduction. Narrative review syntheses, systematic reviews, opinion papers, letters to the editor, and any study not including a primary data/or clear method of data analysis (determined after assessment of methodological quality), will be excluded. In case of duplicate publications from the same study, the most recent or most comprehensive publication will be included.

Information search and search strategy

A comprehensive search strategy for identifying literature relevant to this review has been developed and piloted (See appendix 1). This strategy was developed in accordance with the

Cochrane handbook for systematic reviews of interventions [27], and the Centre for reviews and Dissemination recommendations for Health care review [28]. With this strategy, a search of bibliographic databases and grey literature will be conducted. The following databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Ovid MEDLINE, ProQuest health and medical complete, Allied and Complementary Medicine Database (AMED), Web of Science Core Collection, and Physiotherapy Evidence Database(PEDRO) will be searched. Also trial registers and directory of open-Access repository websites including http:/www.clinicaltrial.gov, http://www.opendor.org, and Web of science conference proceeding will be searched. Additional searches will be performed on relevant studies identified from reference lists.

Study records and data management

Literature search results will be exported into RefWorks^{TM} to check for duplication of studies, and subsequently to facilitate collaboration among reviewers during the process of study selection. Based on prior criteria, eligibility questions and forms for the studies inclusion to the two levels of eligibility assessment will then be developed, piloted, and if required, refined. Bibliographic records will be exported from RefWorks^{TM} into Microsoft excel [29], to facilitate the management selection of articles for inclusion. The review team will then develop, pilot, and if required, refine eligibility questions for the study inclusion within the review.

Selection processes

Initial screening will be conducted first on the study title and then on the abstract by one review author to identify potentially relevant studies. A second review author will then cross-check these initial screening results. Two reviewers will then read through the full length of

selected titles and abstracts for further screening, using the prior eligibility criteria. Any difference of opinion occurring at any stage regarding inclusion or exclusion will be resolved by discussion and reflection, in consultation with a third reviewer if required. Study authors will be contacted (to the maximum of three email attempts) to clarify issues of selection of any study when a decision could not be made based on available information. If an author does not respond, the study will be excluded and the reason for exclusion recorded. Details of the flow of studies throughout the process of assessment of eligibility and studies selection will be represented along with the reasons for exclusion at each stage of the process in a flow chart (PRISMA diagram).

Data collection Processes

Quality appraisal for included studies

The Mixed Methods Appraisal Tool (MMAT) [30] will be employed to assess the quality of included studies. The use of MMAT is to enable a valid, efficient and reliable assessment of the quality of both the quantitative and qualitative studies at the same time [30,31]. Using this tool, the studies will be assessed for the suitability of their study design to the research objectives, risk of bias in included studies, outcome measures, statistical issues, quality of reporting, intervention quality and generalizability of the study results.

Two reviewers will perform the data extraction independently. Any disagreement regarding study eligibility will be resolved by discussion and reflection, in consultation with a third review author if required. The Data Extraction Template developed by the Cochrane Consumers and Communication Review Group [32] will be adapted to extract quantitative data from the quantitative studies. The Supplementary Guidance for Inclusion of Qualitative

Research in Cochrane Systematic Reviews of Interventions [33] will be utilised to extract qualitative data from the included studies.

Data items

Data will be collected from variables including authors reference, participants' characteristics (including age range, gender, inclusion and exclusion criteria), study sample size (also groups sample size where available), criteria used in diagnosing IC, study design, components of the intervention, context of intervention, who delivered the intervention, the duration of intervention and follow-up (where available), attrition rate, outcome(s) assessed, the outcome(s) measurement methods/techniques, results, and conclusions.

Prioritisation of outcomes and justification

For studies with no follow-up, the primary outcome considered will be change in pain following the intervention. Pain has been chosen as the primary outcomes as it may be relevant across diverse pain management interventions, potentially enabling a meta-analysis. Also, this review aims to identify factors that might raise patients' physical activity following pain management interventions for IC. Decreased pain with enhanced physical activity translates into raised effectiveness of these pain management interventions in individuals with IC.

Secondary outcomes will include physical activity behaviour changes post intervention; or adherence to physical activity behaviour changes post intervention for studies with a follow-up period. In addition psychological health outcomes such as self-efficacy, self-esteem, social functioning, and quality of life will be evaluated. The secondary outcomes were selected because they are patients' characteristics that may mediate effect of intervention, and hence

may help in explaining the effectiveness of physical activity improvement and pain reduction. Only data for the first period of outcome assessment will be included for cross-over studies in order to avoid a cross-over effect.

Risk of bias assessment in individual studies

Using the Cochrane Collaboration Tool for Risk of Bias Assessment [27] risk of bias for each of the intervention studies will be evaluated in six key domains: i) selection bias (random sequence generation, allocation concealment); ii) performance bias (blinding - personnel and participants); iii) detection bias (blinding of outcome assessments); iv) bias due to attrition (incomplete outcome data – including drop-outs and withdrawals); v) reporting bias (selective reporting); and v) other bias (other sources of bias not elsewhere addressed). Assessment will be made in each of the included studies and graded as 'high risk' or 'low risk' following a well described procedure [27]. Then, summary assessment for each important outcome (across domains) within and across studies will be conducted [27]. When there is inadequate detail in a study to make a judgement, the risk of bias in that study will be reported as unclear. In such cases, the study authors will be contacted to provide the required information. Two reviewers will make judgements regarding the risk of bias independent of each other. Areas of differences will be resolved by discussion and reflection or in consultation with the third reviewer. Appraisal of the quality of the included studies will only be carried out after study selection has been completed, and during data extraction and synthesis. After this, the strength of evidence for this review will be reported.

RESULTS

The results section of this protocol reports the planned data analysis of the review.

Data synthesis and analysis, including assessment of heterogeneity

A three-phase sequential explanatory synthesis of mixed studies synthesis design will be employed to answer the research questions [30]. First, the question of the effectiveness of pain management interventions for the management of IC will be answered. In doing this, all quantitative studies which examined effectiveness of pain management interventions will be presented, compared, and pooled in an evidence table. The effectiveness of pain management interventions will be established by conducting a meta-analysis of the effects [30]. Data from quantitative studies that cannot be analysed statistically will be interpreted using narrative synthesis.

The second phase will seek to answer question of the attitude, experiences and perspectives of patients to pain management interventions for IC. This will be accomplished using findings from all qualitative studies. In doing this, qualitative thematic analysis will be used to integrate the results of the qualitative studies and the qualitative results of mixed methods studies [30]. Interpretation of this phase will be used establish what patients perceived as beneficial or not beneficial.

Lastly, interpretation of the first and second phases will be carried out to answer the overall objective of the systematic review of the effective components of pain management interventions for improving physical activity in patients with IC. The effective components of the interventions will be inferred by comparing the effectiveness of the interventions that contained the useful components identified from qualitative results with the interventions that did not contain these components.

Characteristics of the retained studies sorted by year of publication will be presented in a tabular form using two different tables [34]. Table 1will describe the interventions studies quantitative data, while table 2 will be for the description of the qualitative studies. Table 1

will have information relating to authors' references, study designs, sample size, gender, age, study objectives, setting (rural vs urban), data collection format, outcomes or themes [34,35]. Table 2 will, in addition, have information on scales used to assess outcome, intervention objectives, components of the intervention, component of the control, format and provider of intervention, setting of intervention (home/community vs hospital), intervention and follow-up periods, and results [34].

Quantitative data analysis/Statistical analysis for Intervention studies

Analysis and presentation of results will be made in hierarchical order with the primary outcomes coming before the additional outcomes. It is anticipated that there may be significant heterogeneity in terms of clinical characteristics of participants, diverse populations studied, different interventions provided, study designs, statistical strategy, and outcomes utilised. Hence heterogeneity will be assessed using the Cochran's χ^2 test, and further quantified using of I^2 [36] in order to make decision on the effect model of meta-analysis to use. It is expected that there will be heterogeneity that cannot readily be dealt with. Consequently, studies with homogenous characteristics in terms of design and comparator will be pooled together for meta-analysis using a random effects model [27]. Other heterogeneous studies will be interpreted using narrative synthesis following the recommendation of Centre for Reviews and Dissemination [27] to explore the relationship in findings between and within the included studies.

In conducting meta-analysis, the statistical approach will be to compare the absolute change in means to the baseline (and the 95% CIs) following intervention or with change in the control groups where baseline data are available. Otherwise, the relative percentage change between post intervention values in the intervention and control groups are compared. The

risk of the outcome in the intervention group will be compared with the control group, with a risk difference calculated from the absolute difference between the treatment and control groups, or the relative risk (or equivalents) for outcome measures that are dichotomous. All adverse effects reported in the included studies will be recoded. All continuous outcomes will be assessed using the weighted mean difference or the standardized mean difference when different measurement scales are used to assess outcome. Skewed data and non-quantitative data will be reported descriptively. Data analysis will use RevMan 5.

Sensitivity analysis: If there are many included quantitative studies with significant heterogeneity in terms of intervention setting (hospital vs home/community based), design (RCTs vs non-RCTs), and intervention type, then subgroup analysis will be implemented to study the potential influence on the treatment effect directions. This will only be conducted if there are more than two studies, and at least two of them are homogenous subset. Subgroup analysis will be limited to the primary outcomes of physical activity and pain.

Publication bias/Meta-biases: To check for metabias, the funnel-plot for asymmetry and the Egger regression test [36] will be conducted. In doing this, data from studies published only as abstracts will be added to the meta-analyses to ascertain if these influenced direction of effect size.

Qualitative data analysis

A thematic approach will be used for synthesis of qualitative research in systematic reviews (Thomas and Harden [37]). This will follow a three stages process. The first stage will be free line-by-line coding of the findings (conclusions) of primary studies. This will be followed by organisation of these 'free codes' into related areas to construct 'descriptive' themes. The last

stage will involve the interpretation and abstraction of the descriptive themes to develop higher order explanations. Synthesis from conclusion/findings, instead of from data, is preferred to enable different qualitative research methods to be combined in a single synthesis of qualitative studies. The review team will validate each of these stages of qualitative analysis by comparing the generated codes and themes with the conclusions/findings of the primary studies.

Rating quality of evidence and strength of recommendations

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be used to judge the quality of evidence of the studies to determine the strength of recommendations in the systematic review, following the approach published by Guyatt et al [38]. Each study will be assessed for study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias. Each study will be rated as high risk of bias or low risk of bias (alternatively a high quality study or a low quality study). Each evidence statement for this review will then be graded from 'High Quality' to 'Very Low Quality' according to the criteria in Table 1 below.

Table 1: Quality of evidence and definitions adapted from Guyatt et al [38]

High Quality	Evidence derived from many studies of high quality such that further research is very unlikely to change our confidence in the estimate of effect
Moderate Quality	Evidence derived from mostly studies of moderate quality and/or few high quality studies such that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low Quality	Evidence derived from mostly low quality studies and/or few studies of moderate quality such that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low Quality	All evidence derived from studies of low quality studies such that any estimate of effect is very uncertain

How this review will be reported

This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement [39], with all items relevant to the review included in the report. A PRISMA checklist applicable to this review will be published with the final report.

Dealing with protocol amendments during the review and after review

In order to avoid the introduction of outcome reporting bias, amendments will not be made on the quantitative aspect of this review protocol based on the findings from the included studies. This precaution is taken because quantitative studies are more easily influenced by publication bias and the manifestations of these biases are more easily assessed. However, any justified unanticipated amendment, possibly arising from a clearer understanding of the review questions, will be documented and implemented by the first author. In the event of this amendment, the report of the review findings, distinction will be made between the initial review question(s) and any subsequent amendment(s) in the report of the review.

DISCUSSION

IC from PAD of the lower extremity is a debilitating condition affecting a range of walking ability, health status and the quality of life of patients [2-4]. Management interventions that target walking limiting pain in this group will be potentially valuable in increasing an individuals' capacity to engage in physical activity. This systematic review will provide evidence in support or against the hypothesis that interventions with a pain management component can be effective for individuals with IC. This conclusion will be derived from a synthesis of the quantitative measurement of pain and physical activity outcomes following pain management interventions and qualitative evidence regarding the effectiveness and patient compliance with pain management interventions. When conducted, the ability of the

review to comment definitively on the topic will be limited by the quantity and quality of available evidence. However overall, the review will clarify the existing evidence base regarding the effect of pain management interventions on physical activity, and allow the selection of effective components of pain management for future tailored intervention.

Protocol registration: This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 04 November 2015 (registration number: CRD42015027912).

Conflict of interest: None declared

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Appendix 1: Search strategy

AMED(EBSCO host)Searched 05/01/2016

S28 S10 AND S19 AND S28
S28 S20 OR S21 S22 OR S23 OR S24 OR S25 OR S26 OR S27
S27 treadmill walking
S26 walking ability
S25 time spent walking
S24 claudication distance
S23 walking distance
S22 physical capacity
S21 physical activity capacity
S20 Physical activity
S19 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR 17 OR S18
S18 transcutaneous electrical stimulation
S17 transcutaneous electric nerve stimulation
S16 transcutaneous electrical nerve stimulation
S15 transcutaneous electrical nerve stimulation (tens)
S14 pain control
S13 pain management
S12 pain medication
S11 pain management interventions
S10 S9 OR S8 OR S7 OR S6 OR S5 OR S4 OR S3 OR S2 OR S1
S9 ischemic lower extremity disease
S8 peripheral arterial occlusive diseases
S7 peripheral arterial diseases (pad) of lower extremities
S6 peripheral vascular diseases
S5 peripheral arterial diseases
S4 intermittent claudication symptoms
S3 intermittent claudication
S2 claudicants
S1 arterial occlusive diseases

PsycINFO (ProQuest host) (1955-2015 Nov). Searched 02/01/2016

("intermittent claudication" OR "claudicants") AND ("pain management" OR "pain management intervention" OR "pain medication" OR "pain chemotherapy") OR ("transcutaneous electric nerve stimulation" OR "transcutaneous electrical nerve stimulation" OR "effect of transcutaneous electrical nerve stimulation" OR "transcutaneous nerve stimulation") AND ("physical activity" OR "walking" OR "physical activity capacity" OR "walking capacity") OR ("walking distance" OR "claudication distance" OR "time spent walking")

ProQuest Research Library. Searched 04/01/2016

("intermittent claudication" OR claudicants) AND ("pain management" OR "pain management intervention" OR "transcutaneous electrical nerve stimulation" OR "transcutaneous electric nerve stimulation") AND ("physical activity" OR "physical activity capacity" OR "walking capacity" OR "functional capacity") OR ("walking distance" OR "claudication distance")

PEDro database **Searched 01/01/2016**

1. Intermittent claudication* pain management* physical activity*
2. Ischemic leg pain* pain therapy* physical activity
3. Intermittent claudication* transcutaneous electrical nerve stimulation* physical function*
4. Intermittent claudication* transcutaneous electrical nerve stimulation* physical activity*
5. Intermittent claudication* transcutaneous electrical nerve stimulation* walking distance*

ScienceDirect Searched 03/01/2016
"intermittent claudication" OR claudicants AND "pain management" OR "pain management intervention" OR "transcutaneous electrical nerve stimulation" OR "transcutaneous electric nerve stimulation" OR anaesthesia" AND "physical activity" OR "claudication distance" OR "physical activity capacity" OR "walking capacity" OR "functional capacity" OR "walking distance"

Ovid® Searched 06/01/2016

16	4 AND 8 AND 15
15	9 OR 10 OR 11OR 12 OR 13 OR 14
14	claudication distance. mp.
13	exp walking/ OR walking distance.mp
12	walking distance.mp
11	walking capacity.mp
10	Exercise tolerance/OR physical capacity.mp
9	physical activity.MP. OR exp motor activity/
8	5 OR 6 OR 7
7	transcutaneous electrical nerve stimulation.mp
6	exp transcutanous electrical nerve stimulation.mp
5	exp pain management/ OR pain management intervention*.mp.
4	1 OR 2 OR 3
3	exp peripheral arterial diseases/or exp peripheral vascular diseases/ OR exp arterial occlusive diseases/
2	claudicant*. Mp
1	intermittent claudication.mp. OR exp intermittent claudication

CINAHL Searched 03/01/2016

S23	S4 AND S12 AND S22
S22	S13 S14 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
S21	"Treadmill walking"
S20	"Walking ability"
S19	"Claudication index"
S18	"Time spent walking"
S17	"Claudication distance"
S16	MH "Walking+") OR "walking distance"
S15	"physical activity capacity"
S14	"walking capacity"
S13	(MH "physical activity")
S12	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S11	"transcutaneous electrical nerve stimulation"
S10	"pain medication"

S9 “pain management”
S8 (MH “transcutaneous electrical nerve stimulation (Iowa NIC)”) OR (MH “transcutaneous electric nerve stimulation”)
S7 (MH “anagelsia”)
S6 (MH “pain control”(Saba CCC)”)
S5 (MH “pain management (Iowa NIC)”)
S4 S1 OR S2 OR S3
S3 (MH “peripheral arterial diseases”)
S2 (MH “intermittent claudication”)
S1 (MH “arterial occlusive diseases”) (MH “peripheral vascular diseases”)

MEDLINE®(ProQuest host)04/01/2016
(intermittent claudication) OR (vascular claudication OR claudicants) AND (transcutaneous electric nerve stimulation OR transcutaneous electric nerve stimulation) OR (pain management interventions OR pain relief) OR (pain medication OR pain management) AND (physical activity OR physical activity capacity) OR (walking capacity OR walking distance) OR (claudication distance OR walking ability) OR (time spent walking)

ISI Web of Science**Searched 07/01/2016**

1. (Intermittent claudication* or peripheral arterial occlusion* or peripheral arterial disease* or peripheral vascular claudication*)
2. (pain management* or intervention* or trial* or effect* or efficacy* or effectiveness* or pain management or pain medication* transcutaneous electrical nerve stimulation* transcutaneous electric nerve stimulation* transcutaneous electrical stimulation* peripheral vascular disease education* health education*)
3. (control group* or medical intervention* or other intervention* or usual care*)
4. (physical activity* claudication distance* or physical activity capacity* or walking ability* or walking distance)
5. #1 AND #2 AND #3 AND #4(Intervention studies)
6. #1 AND #2 AND #3 AND #4(Qualitative studies)
7. #1 AND #2 AND #3 AND #4(Observational studies)